Invasive infections caused by *Blastoschizomyces capitatus* and *Scedosporium* spp.

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ABSTRACT

Blastoschizomyces capitatus, Scedosporium prolificans and *S. apiospermum* are emerging fungal pathogens that may cause disseminated disease in neutropenic patients. They can present as fever resistant to antibiotics and to wide-spectrum antifungal agents, although they may involve almost every organ. The proportion of recovery from blood cultures is high and they are characteristically resistant to most antifungal agents. Prognosis is poor unless patients recover from neutropenia. Voriconazole has good in-vitro activity and is currently the drug of choice for these infections.

Keywords *Blastoschizomyces capitatus*, *Scedosporium prolificans*, *S. apiospermum*, opportunistic infection invasive mycosis, neutropenia

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BLASTOSCHIZOMYCES CAPITATUS

The fungus known as *Blastoschizomyces capitatus* was previously known as *Trichosporon capitatum*, *Geotrichum capitatum* and *Blastoschizomyces pseudotrichosporom*, and was considered a new genus in 1985 after the suggestion by Salkin and colleagues [1]. It is a yeast-like fungus that forms creamy, wrinkled colonies and grows in conventional media, including Sabouraud, but which is resistant to cycloheximide. Its principal characteristic is the production of annelloconidia which, after schizogonic division, develop structures similar to arthroconidia. It can be identified by conventional commercial products, it is incapable of using potassium nitrate as its only source of nitrogen and it is incapable of assimilating a large number of carbohydrates. *B. capitatus* has been characterised by molecular methods and differentiated from similar fungi [2–4].

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Epidemiology

B. capitatus can be isolated in nature and the environment and is capable of colonising the mucosa and the skin of some patients. It was not considered as a pathogenic fungus until 25 years ago. It has been isolated in sputum, faeces, oral mucosa, skin and liquids for intravenous infusion as well as in environmental samples [5–10]. It is a potential cause of mastitis in cattle [11].

In a study involving 353 immunocompromised patients, the presence of colonisation and infection by *B. capitatus* was sought over a 37-month period. Thirteen (3.7%) cases had developed colonies in stool, skin, or urine and three of these 13 developed systemic infection [12].

B. capitatus can produce dermatomycosis, onychomycosis [13–15] and some deep localised lesions, but its greatest danger lies in its capacity to cause disseminated and invasive mycoses, particularly in severely immunodepressed patients. Neutropenia is the most important predisposing factor, followed by the use of corticosteroids and other immunodepressors.

Experimental models were obtained initially in rabbits and later in other animals, including irradiated mice, in which heart and kidney abscesses appeared relatively easily after intravenous infusion [6,16,17].

In one of the most important series, published by Martino *et al*. [8], the authors report 21 patients over a 30-month period, of whom 12 were infected, four were possibly infected and five were colonised.

The invasive and disseminated disease almost only affects patients with haematological disorders, who are undergoing chemotherapy during periods of profound neutropenia. It usually presents with fever, and is generally resistant to antibiotics and sometimes to antifungals such as azole derivatives or amphotericin B. It can present with cutaneous lesions, sometimes in the form of a disseminated maculo-papular rash, or it can appear with catheter-related sepsis or focal lesions [8].

Other clinical manifestations can include cough, expectoration, chest pain, spontaneous pneumothorax, pulmonary infiltrates and jaundice. In some patients with hepatosplenic involvement it cannot be distinguished clinically from hepatosplenic candidiasis [8,18,19].

It has been reported as a pulmonary pathogen [6] and also as affecting the gastrointestinal tract [20], kidney and liver [8,21] (Fig. 1).

It can present by invading the central nervous system, either in the form of localised lesions or as meningitis or encephalitis [22].

Occasionally, it presents with endocarditis, generally in disseminated disease in the neutropenic patient, but also as a disease which appears to have been contracted in the operating theatre in immunodepressed patients undergoing valve replacement with extracorporeal surgery [3,8,23,24].

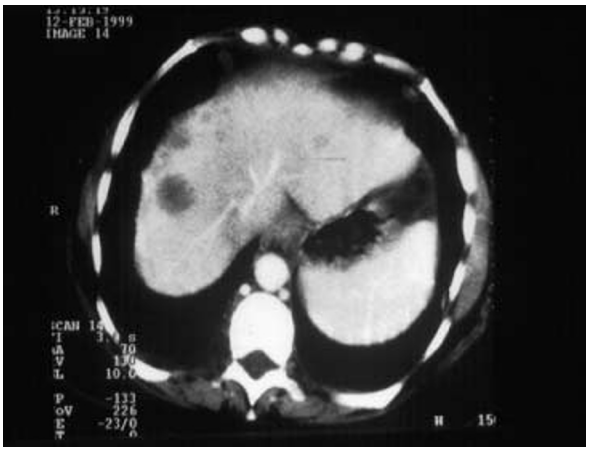

Fig. 1. Hepatic lesions caused by *Blastoschizomyces capitatus* in a patient with leukaemia.

As far as osteoarticular manifestations are concerned, *B. capitatus* has been described as a cause of mandibular osteomyelitis in a patient with lymphoma [25] and as the cause of single or multiple spondylodiscitis with or without paraverterbral abscesses [26–28].

B. capitatus may be the cause of funguria in some patients [29].

Of all the possible pictures, the most common is disseminated and multifocal infection which is almost always diagnosed by the presence of positive blood cultures in more than 90% of cases [3,8,18,20–22,24–28,30–49].

Outside the context of the neutropenic patient, there have been reports of cases of disseminated infection by *B. capitatus* in an intravenous drug user [48].

Laboratory

The diagnosis of invasive *B. capitatus* infection is based on its isolation from normally sterile organic fluids or tissues. As mentioned above, the fungus grows by forming white to cream-coloured colonies, which are yeast-like, wrinkled, shiny or opaque in appearance. Microscopy reveals well-developed hyphae and pseudohyphae with aneloconidia and blastospores. Fermentation tests are negative and the fungus only assimilates glucose and galactose. The micro-organism is urease-negative and resistant to cycloheximide and capable of growing at 42 °C [1,50].

Unlike *Trichosporon beigelii*, there are no cross-reactions with the latex test for the detection of cryptococcal antigen [8] in patients infected with *B. capitatus*.

Data on in-vitro sensitivity tests are somewhat sparse in the literature; they are usually performed with a low number of strains and they occasionally provide contradictory and variable information. in-vitro, the micro-organism is usually sensitive to amphotericin B and 5-flucytosine [24] and more variable to fluconazole and other azole derivatives [2,32,44,51].

A sensitivity study of six strains of *B. capitatus* isolated in Spain revealed the following values of the minimum 50% and 90% inhibition concentrations (MIC_{50} and MIC_{90}): amphotericin B (0.25 and 0.50, respectively), fluconazole (2 and 8), itraconazole (0.06 and 0.25), ketoconazole (0.06 and 0.25) and 5FC (< 0.03 and > 64). In another

Table 1. In-vitro sensitivity data of four *B. capitatus* isolates

Drug	Dose	Range	MIC_{50}	MIC_{90}
AM B	2 μg/mL	1–4	2	4
5-FC	8 μg/mL	0.12–0.25	0.12	0.25
KETO	1 μg/mL	0.5–1	1	1
FLU	16 μg/mL	16–32	32	32
ITRA	0.25 μg/mL	0.5–1	1	1
VORI	–	0.12–0.5	0.25	0.5
LY-303366	–	1–4	4	4

AM B, amphtericin B; 5-FC, 5-flucytosine; KETO, ketoconazole; FLU, fluconazole; ITRA, itraconazole; VORI, voriconazole; anidulafungin.

study on the four strains causing invasive disease in our centre, the MICs were as follows: amphotericin (2 μg/mL), fluconazole (32 μg/mL), 5-flucytosine (0.12–0.25 μg/mL), ketoconazole (0.5–1 μg/mL), itraconazole (0.5–1 μg/mL) and voriconazole (0.12–0.5 μg/mL) [18] (Table 1).

Among the new drugs, voriconazole has shown good activity in-vitro against *B. capitatus*, but there is no information on caspofungin as it is difficult to obtain suitable powder from the manufacturer to carry out in-vitro tests [52].

Sordarins have shown good in-vitro activity against *B. capitatus* [53,54].

In some patients, despite in-vitro sensitivity, disease may occur even after prophylaxis with different antifungal drugs [39,45].

Immunoblots enable us to detect the presence of antibodies both in infected patients and in control patients [55], and are therefore not considered very useful from a diagnostic point of view.

Treatment and outcome

The outcome of invasive disease caused by *B. capitatus* depends mainly on patient immunity. In patients with profound neutropenia, mortality is greater than 90% and survival has largely coincided with the recovery of the neutrophil count. The most common antifungal regimen to date has been amphotericin B, either alone or in association with other drugs, mainly with 5-flucytosine. In isolated cases, the association of neutrophils or neutrophils and macrophage-stimulating factors, and the addition of treatment with interferon-γ, seem to be efficacious, but the evidence of their usefulness is totally inconclusive [8,33,38]. In catheter-related infections, it is essential to remove the catheter. When the disease is local and can be treated by surgery, the role of surgery is essential.

INFECTIONS CAUSED BY *SCEDOSPORIUM* SPECIES

The filamentous fungus *Scedosporium* consists of two species, *S. prolificans* and *S. apiospermum*. Both can cause invasive infections in immunocompromised patients with a very poor prognosis. Therapy of these infections is especially difficult because of their broad resistance to many antifungal agents, including amphotericin B.

Scedosporium prolificans

Severe fungal infections are especially common in immunosuppressed patients, particularly in those with prolonged neutropenia. *Candida*, *Aspergillus* and zygomycetes are the most frequently encountered micro-organisms. However, new agents are continuously being included in the list of opportunistic fungal pathogens [50]. *S. prolificans* is the most common cause of disseminated phaeohyphomycosis (infection caused by dematiaceous fungi). A total of 30 cases have recently been reviewed [56].

Micro-organism

S. prolificans was first described in 1984 by Malloch and Salkin in a child with osteomyelitis. It was then called *S. inflatum* and clear identification criteria were established some years later. At present, *S. prolificans* is preferred, because of DNA similarities with *Lomentospora prolificans* [57]. Identification is based mainly on the morphological characteristics of the asexual structures produced by the fungus in culture (Fig. 2).

The organism is resistant to most antifungal agents, including amphotericin B, 5-flucytosine and imidazoles [58]. New triazoles (UR-9825 and voriconazole) have been found to have some activity in-vitro [59], although these data have not been confirmed by other authors [60].

Epidemiology

S. prolificans is a ubiquitous fungus present in soil. Although its distribution is universal, most cases have been reported in Spain and Australia [56,61,62].

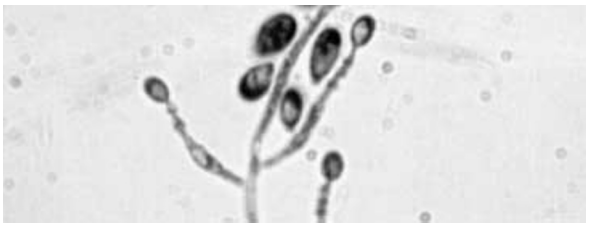

Fig. 2. Flask-shaped annelloconidia of *S. prolificans* forming clusters at the ends of annellides with swollen bases (lactophenol-cotton blue stain).

Most clinical cases are sporadic and may appear both in immunocompetent and in immunocompromised patients. The main risk factors in immunocompetent patients are surgery and trauma. In immunosuppressed patients, the most important risk factor is prolonged profound neutropenia [63–66]. Persistent neutropenia was described in 90% of patients with disseminated infection [56], and lung transplant, prosthetic heart valve, and human immunodeficiency virus (HIV) infection have also been reported as underlying conditions [56,65–67]. It may also colonise the airway of patients with cystic fibrosis [66].

Some small outbreaks have been reported [68–70]. In one of the outbreaks, six inpatients with acute nonlymphocytic leukaemia died as a result of invasive infection with *S. prolificans*. Phenotypic and genotypic assessment of samples from clinical material and ambient air from the isolation rooms where the patients were being treated showed that the epidemic was caused by a single strain. After implementation of aerial control measures, there were no further infections with this organism [69]. In another report, the fungus was recovered from the air in the room of a patient with leukaemia and disseminated infection [71]. Fingerprinting by randomly amplified polymorphic DNA analysis is a useful tool for the analysis of possible outbreaks [72,73].

Clinical manifestations

In immunocompetent patients *S. prolificans* may cause locally invasive infections, which are usually osteoarticular and related to trauma or surgery [61]. Cases of keratouveitis associated with the intraocular long-term retention of a contact lens [74] or pulmonary infection secondary to long-standing bronchiectasis have also been described [75].

The most common presentation of *S. prolificans* infection in immunocompromised patients is fever unresponsive to broad-spectrum antimicrobial agents [61]. In many of the cases, the patients were already receiving systemic antifungal agents when the infection was diagnosed.

The infection may involve the lung, the skin and almost every organ. Endophthalmitis, renal and splenic abscesses, meningoencephalitis, endocarditis and many other manifestations have been reported [56,61,76]. In a recent series from Spain, 37% of the patients had central nervous system involvement and 25% had skin lesions [61]. Skin lesions may appear as papular rash, papules, or nodules that may become necrotic.

Infection by *S. prolificans* can be differentiated from invasive aspergillosis by its higher tendency to produce skin lesions and to be recovered from blood cultures. Interestingly, 80% of disseminated infections with *S. prolificans* were associated with positive blood cultures [56]. The diagnosis requires isolation in culture, since its histological appearance is similar to that of *Aspergillus*.

Treatment

Focal infections in immunocompetent hosts respond well to surgery and antifungal drugs, but systemic *S. prolificans* infection treatment is difficult. Optimal treatment of *S. prolificans* infection remains controversial because of the resistance of the micro-organism to practically all available antifungal agents. Although many antifungal agents have been used, no single drug was associated with improved outcome.

At present, treatment involves amphotericin or voriconazole, granulocyte colony-stimulating factor in neutropenic patients and surgical debridement when feasible. Polymorphonuclear leukocytes synergize with antifungal agents against this micro-organism [77], so the reversal of neutropenia may have important therapeutic implications [78].

Some new approaches for the treatment of infections caused by this micro-organism have been studied. Terbinafine has been shown to have in-vitro activity against dematiaceous fungi. The combination of terbinafine and the azoles voriconazole, miconazole and itraconazole against five clinical *S. prolificans* isolates showed a synergistic effect [79].

The in-vitro interaction between amphotericin B and pentamidine against 30 clinical isolates was evaluated using a checkerboard microdilution

method. Amphotericin B alone was inactive against all the isolates. The combination was synergistic against 28 out of 30 isolates (93.3–100% depending on the method), and antagonism was not observed [80].

Recovery from neutropenia is critical, and mortality is essentially 100% in patients with persistent neutropenia [56]. The disease is usually rapidly fatal, and most patients die within 4 days of the first positive blood culture [61].

Scedosporium apiospermum

S. apiospermum is a saprophytic fungus isolated worldwide from soil and plant residues. Although the organism has shown low inherent virulence, an increasing number of invasive infections caused by this micro-organism have been reported in the last few years, mainly in patients with haematological malignancies or solid organ transplantation.

Micro-organism

S. apiospermum (the anamorph state of *Pseudallescheria boydii*) is a hyaline filamentous fungus, ubiquitously present in soil, sewage and polluted waters.

P. boydii is characterised microbiologically by terminal annelloconidia and characteristic cleistothecia in the sexual state (teleomorph form). The asexual state (synanamorph) of *P. boydii* without cleistothecia are designated *S. apiospermum*.

The fungus grows well on standard mycological culture media. In a few days, the mould colony takes on a tan colour and produces characteristic sporulating structures. No serology is available, although isolation of *S. apiospermum* from a sterile site is diagnostic. The proportion of positive blood cultures is much lower than for *S. prolificans*.

Regarding antimicrobial susceptibility, *S. apiospermum* isolates are more susceptible in-vitro than *S. prolificans*, with the highest activity exhibited by voriconazole (MIC_{90}, 0.5 μg/mL), followed by miconazole (MIC_{90}, 1 μg/mL), UR-9825 and posaconazole (MIC_{90}, 2 μg/mL), and itraconazole (MIC_{90}, 4 μg/mL). The MICs of terbinafine, amphotericin B and the two formulations of nystatin (for which no statistically significant differences in antifungal activities were found for the two species) for *S. apiospermum* isolates were high. Cross-resistance was observed among all the azoles except posaconazole, and among all the polyenes except the lipid formulation [81].

Epidemiology

Invasive disease caused by *S. apiospermum* has been described in solid organ transplant recipients [67,82–88], patients with haematological malignancies [89], after haematopoietic stem cell transplantation [90], in conjunction with chronic corticosteroid therapy [91], and in patients with HIV infection [92–94], nephritic syndrome [95], or chronic granulomatous disease [96,97] among others. Invasive mycoses after near-drowning have been classically related to this fungus [98].

Typing by polymerase chain reaction amplification of ribosomal intergenic spacer sequences has been used in molecular epidemiological studies in patients with chronic lung disease [99].

The principal portal of entry is the respiratory tract or the skin by trauma, from where it may cause widespread dissemination.

Clinical manifestations

This micro-organism is an uncommon cause of human infection. In normal hosts it usually produces localised disease after penetrating trauma or disseminated infection after aspiration of polluted water. There have been reports of keratitis after trauma or surgery and even without previous ocular injury [100–103], in conjunction with chorioretinitis [104], vertebral osteomyelitis [105], post-traumatic cranial infection [106], lymphocutaneous syndrome [107], lymphadenitis [108] and septic arthritis [109]. A case of disseminated fatal disease after a post-traumatic osteomyelitis has also been described [110]. *S. apiospermum* may also colonise the respiratory tract of patients with cystic fibrosis [111,112].

However, in immunocompromised patients it may cause severe pulmonary or disseminated infections. In patients undergoing continuous ambulatory peritoneal dialysis it can cause pneumonia [83,93], mycetoma [113], sternal wound infection [83], brain abscess [85,90,91,114,115], sinusitis [94], endocarditis [116], skin lesions [85,86,91,117–120], orchitis [87], malignant otitis externa [92], fungemia [84], mycotic aneurysm [121] and peritonitis [122]. Central nervous system involvement is disproportionately common in patients with pseudallescheriasis when compared with many other mycoses.

Many patients are already receiving systemic antifungal therapy when the infection is diagnosed [90], with the result that it is described as breakthrough mycoses.

Recently, 23 cases of solid organ transplant patients have been reviewed [82]. The 23 patients included liver (4), kidney (8), heart (8), lung (2), and heart/lung (1) recipients. The disease was more common in males (19 : 4) and was diagnosed at a median of 4 months (range, 0.4–156 months) after transplant. The clinical presentation included disseminated disease (8), skin lesions (3), lung disease (5), endophthalmitis (1), meningitis (1), brain abscess with or without extension to the eye (3), fungal mycotic aneurysm (1), and sinusitis (1). Seven (30%) patients had intravascular infection, and 11 (48%) patients had central nervous system involvement. Antifungal therapy was accompanied by surgical debridement in nine cases. Three additional patients were found to have airway colonisation only and received itraconazole prophylaxis, without evidence of disease. Of 22 patients with known outcome, 16 (72.7%) died. Five of six patients who survived had localised infections: skin lesions ($n = 3$), sinus fungus ball ($n = 1$), and solitary lung nodule ($n = 1$). All patients with disseminated disease and 10 of 11 patients with central nervous system disease died. An exception was one patient with a brain abscess who was successfully treated with voriconazole and surgical drainage.

In a review of 31 reported cases of invasive infection, 61% died despite antifungal therapy [84]. Of eight patients with localised musculoskeletal soft tissue infection, seven required surgery, and three underwent amputation.

The correct diagnosis of *S. apiospermum* infection must be confirmed by the isolation of this fungus in culture, since both its histological appearance and clinical presentation are quite similar to those of *Aspergillus*. A mistaken diagnosis can result in delayed or inappropriate treatment, considering that *S. apiospermum* is almost always resistant to amphotericin B. Microbiological diagnosis is easy, as a result of its macro- and microscopic appearance in culture.

S. apiospermum should be included in the differential diagnosis of any manifestation compatible with invasive mycosis in immunosuppresed patients, mainly when treatment with amphotericin B or itraconazole has failed.

Treatment

The management of invasive *S. apiospermum* infections is difficult because of this fungus's intrinsic resistance to many antifungal agents, including fluconazole and amphotericin B [123]. An early aetiologic diagnosis by culture is thus of the utmost importance.

The treatment of choice for these infections has not been established. Surgical resection, when possible, and antifungal therapy with azole derivatives (mainly itraconazole) have been successful in some cases [97,124–126]. However, other patients have shown no response to itraconazole despite in-vitro susceptibility [127]. Most strains are resistant to amphotericin B.

Miconazole has been used in some cases of *S. apiospermum* infection [100]. However, considering the high toxicity of this compound, the difficulty in obtaining intravenous miconazole (not commercially available), and the high rate of recurrence of infection and mortality, it is not recommended at present.

Voriconazole is a new triazole with good in-vitro activity against a range of moulds, including *S. apiospermum* [60]. The good in-vitro activity and satisfactory experience in patients after antifungal drug therapy mean that voriconazole is currently the drug of choice for this infection [91,115,128–130].

Mellinghoff *et al*. have recently reported the case of a 41-year-old man with acute lymphoblastic leukaemia who developed multiple *S. apiospermum* brain abscesses. The infection progressed despite neurosurgical drainage and treatment with itraconazole, amphotericin B and ketoconazole, but the brain abscesses resolved completely after treatment with posaconazole alone [114]. New therapeutic options are being explored [131]. Caspofungin may also have in-vitro activity against this fungus [90].

The use of granulocyte colony-stimulating factors has been advocated as a potentially useful tool in the treatment of very severe fungal infections, even in non-neutropenic patients. It increases neutrophil production and enhances polymorphonuclear lymphocyte-mediated killing of fungal pathogens *in vivo*, thereby implicating a possible therapeutic role as a biological response-modifying agent during opportunistic fungal infection. It should be used for short-term treatments and in very severe cases until more information is available.

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